

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 295/32, A61K 31/495	A1	(11) International Publication Number: WO 98/25914 (43) International Publication Date: 18 June 1998 (18.06.98)
(21) International Application Number: PCT/JP97/04451 (22) International Filing Date: 5 December 1997 (05.12.97) (30) Priority Data: 8/331784 12 December 1996 (12.12.96) JP (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): KITAMURA, Satoshi [JP/JP]; 45-B-814, Yamadaminami, Suita-shi, Osaka 565 (JP). MIMURA, Hisashi [JP/JP]; 4-12-8, Fujiwaradainakamachi, Kita-ku, Kobe-shi, Hyogo 651-13 (JP). YAMASAKI, Hiroshi [JP/JP]; 3-17-10, Hinomine, Kita-ku, Kobe-shi, Hyogo 651-12 (JP). BABA, Yukihiisa [JP/JP]; 1-27-12-103, Mukonosohigashi, Amagasaki-shi, Hyogo 661 (JP). (74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).		(81) Designated States: AU, CA, CN, HU, IL, JP, KR, MX, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: N-(4-ACETYL-1-PIPERAZINYL)-4-FLUOROBENZAMIDE HYDRATE (57) Abstract The invention has for its object to provide N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide in a form easy to handle and stable against stress testings. N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide hydrate is easy to handle under ordinary interior humidity conditions and stable against accelerated heat, humidity, and light exposure test conditions.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

DESCRIPTION

N-(4-ACETYL-1-PIPERAZINYL)-4-FLUOROBENZAMIDE HYDRATE

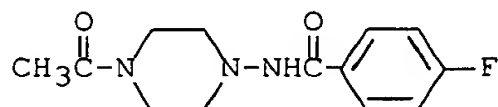
5 TECHNICAL FIELD

This invention relates to N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate which is useful as a medicament.

BACKGROUND ART

10 N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide having the following chemical formula:

15



20

was first described by the applicant of the instant application in WO 91/01979 and is a per se known compound. This compound has the potentiation of the cholinergic activity and is known to have excellent antidementia and antiamnesic actions.

DISCLOSURE OF INVENTION

25

This invention relates to N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate.

30

One object of this invention is to provide N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide in a form easy to handle under ordinary interior humidity conditions and resistant to stress testings, i.e. N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate.

35

Another object of this invention is to provide an agent and a pharmaceutical composition comprising, as an active ingredient, said hydrate.

A further object of this invention is to provide a

therapeutical method for the treatment and/or prevention of disorders in the central nervous system for human beings, and more particularly in the treatment and/or prevention of amnesia, dementia, senile dementia and the like.

5

More particularly, the inventors of this invention endeavored in earnest to accomplish the above object and discovered the hydrate form of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide which can be handled with ease under ordinary interior humidity conditions and stable even under accelerated heat, humidity, and light exposure test conditions. This invention has been accomplished on the basis of the above finding.

10

15

20

25

30

35

Thus, N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide free of water of crystallization undergoes change in water content by absorbing moisture under ordinary interior humidity conditions and the rate of its moisture absorption also varies with the ambient relative humidity, thus offering the disadvantage that it cannot be easily handled in the laboratory room and the pharmaceutical manufacturing room. Therefore, the inventors explored for a stable form of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide which would show little change in water content under ordinary interior humidity conditions and could, therefore, be easily handled in both the laboratory room and the pharmaceutical manufacturing room and discovered that the hydrate, preferably the monohydrate (theoretical water content 6.36%), of the above compound shows substantially no change in water content in addition to the advantage that it can be easily handled. Furthermore, this N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate, preferably monohydrate thereof, is chemically stable even under accelerated heat, humidity, and light exposure test conditions. It was also confirmed that N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate, preferably monohydrate thereof, remains chemically stable

without undergoing crystallographic change in the accelerated heat, humidity, and light exposure tests. The following are experimental findings substantiating the above description.

In this invention, it is to be noted that N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate may include all hydrate containing one or more water molecule(s) such as monohydrate, dihydrate, trihydrate, etc., in which preferable one is monohydrate.

Experiment 1: Moisture absorption test

1) Method

About 0.2 g of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate was accurately weighed into a weighing bottle about 3 cm in diameter and placed in a desiccator controlled at a relative humidity (R.H.) value of 43% with a saturated potassium carbonate solution. This test sample was stored in a constant-temperature room at 25°C for 24 hours and the change in water content was sequentially monitored.

2) Results

Table 1

Time (Hr)	0	1	2	3	4	5	6	24
Water content (%)	6.23	6.23	6.23	6.27	6.23	6.27	6.23	6.18

The above results indicate that N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate undergoes little change in water content in an environment of 43% R.H. even for as many as 24 hours.

Experiment 2: Stability in solid state

1) Method

N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate, 0.2 g, was weighed into an amber-colored No. 1 bottle which was then placed in a desiccator controlled at 75% R.H. with a saturated aqueous solution of sodium chloride and stirred in a minijet oven at 70°C for 9 days. Separately, 0.2 g of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate was accurately weighed, spread thinly in a dish about 4 cm in diameter, covered with polyvinylidene chloride film, and exposed to a chemical lamp for 24 hours. Using the above 2 samples, the quality parameters of description, water content (K.F. method), infrared spectrum, and liquid chromatographic assay [detector: ultraviolet spectrophotometer (exciting wavelength 254 nm), column: TSK gel ODS-80TM (5 µm) (4.6 mm in. dia. x 15 cm long), column temperature: room temperature; mobile phase: water-acetonitrile (4:1), sample concentration: 0.5 mg/ml (solvent: acetonitrile), flow rate: the retention time of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide adjusted to ca 7 min.) (ca 1.0 ml/min.), injection size: 5 µl] were determined.

2) Results

Table 1

Storage conditions	Initial	70°C 75% R.H., 9 days	Chemical lamp exposure test, 24 hrs
Description	White powders	White powders	White powders
Water content (%)	6.23	6.40	6.10
IR spectrum	-	No change	No change
Residue (%)	100.0	100.5	99.9

Those results indicate that N-(4-acetyl-1-piperazinyl)-

4-fluorobenzamide monohydrate is chemically stable against accelerated 70°C, 75% R.H. heat and humidity test and accelerated chemical lamp exposure test conditions, undergoing no change in crystal morphology.

Example 1

N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide (192.0 g) is added to 50% aqueous ethanol (960 ml) and dissolved therein by heating. The solution is filtered when hot and washed with prewarmed 25% aqueous ethanol (384 ml). Then, water (1540 ml) is added under warming and the mixture is cooled gradually under constant stirring. The resulting crystals are collected by filtration and dried in vacuo. The anhydrous N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide thus obtained is allowed to stand for equilibration under a water-filled tray disposed in the bottom stage of a dryer at a shelf temperature of 25°C and a vacuum of 25-30 mmHg to provide N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate (183.5 g).

Water content (K.F. method):

6.23% (theoretical value for the monohydrate: 6.36%)

Infrared (IR) spectrum (Nujol)

As shown in Fig. 1.

Powder X-ray diffraction pattern

As shown in Fig. 2.

Thermal analysis (TG/DTA data)

As shown in Fig. 3

By subjecting the compound obtained by the above procedure to recrystallization from a saturated chloroform solution, colorless clear platelets can be obtained. X-ray crystallographic analysis of the above crystal crop yielded the crystal structure containing one molecule of water as shown in Fig. 4 and the X-ray diffraction pattern (Fig. 5)

calculated from this crystal structure was found to agree well with the powder X-ray diffraction pattern shown in Fig. 2.

5 Effects of the Invention

N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide hydrate as provided by this invention undergoes little change in water content under ordinary interior humidity conditions and can, therefore, be easily handled. It has also been established
10 that the hydrate is chemically stable against accelerated heat, humidity and light exposure test conditions, showing no alteration in crystal morphology, either.

For therapeutic purpose, N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate of the present invention can be used
15 in a form of pharmaceutical preparation containing said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral,
20 parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension or emulsion. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers
25 and other commonly used additives.

While the dosage of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of
30 N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide hydrate may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

35 BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1: An infrared absorption spectrum of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate.

Fig. 2: A powder X-ray diffraction pattern of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate.

Fig. 3: A thermal analysis (TG/DTA) diagram of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate.

Fig. 4: The three-dimensional structure of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate.

Fig. 5: The X-ray diffraction pattern calculated from the 3-dimensional structure of N-(4-acetyl-1-piperazinyl)-4-fluorobenzamide monohydrate.

CLAIMS

1. N-(4-Acetyl-1-piperazinyl-4-fluorobenzamide hydrate

5 2. The monohydrate according to claim 1.

3. The monohydrate according to claim 2 which has the following physical constants:

10 (i) a powder X-ray diffraction pattern with characteristic peaks around 7.0°, 13.8°, 17.7°, 22.0°, 24.4° and 26.1°

(ii) an infrared spectrum (Nujol) with absorption bands near 3196, 1641, 1618, 1240 and 849 (cm⁻¹)

15

4. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.

20

5. A compound of claim 1 for use as a medicament.

25

6. A method of therapeutic treatment and/or prevention of amnesia, dementia or senile dementia which comprising an effective amount of a compound of claim 1 to human beings.

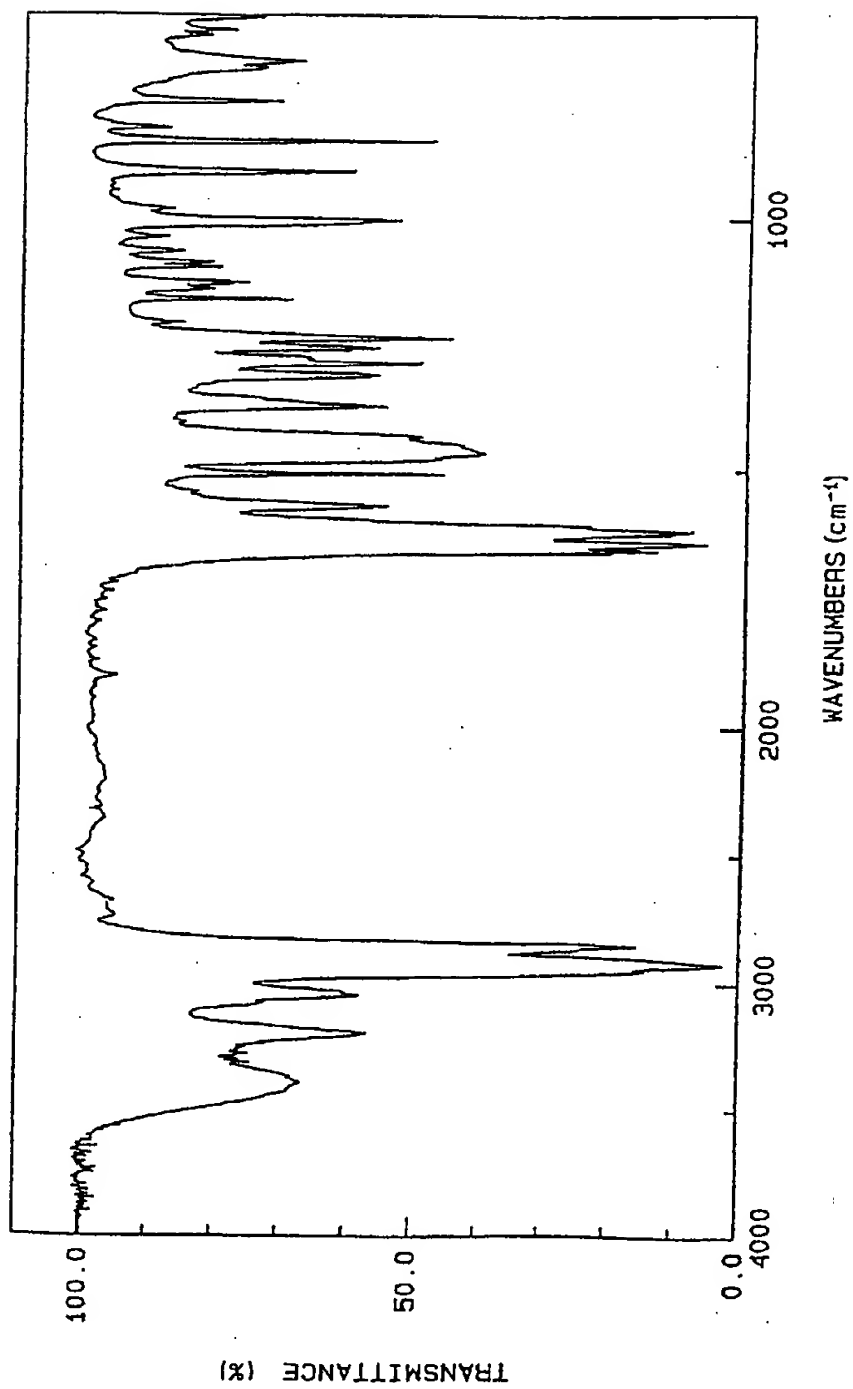
30

7. Use of a compound of claim 1 for the manufacture of a medicament for treating and/or preventing amnesia, dementia or senile dementia in human beings.

35

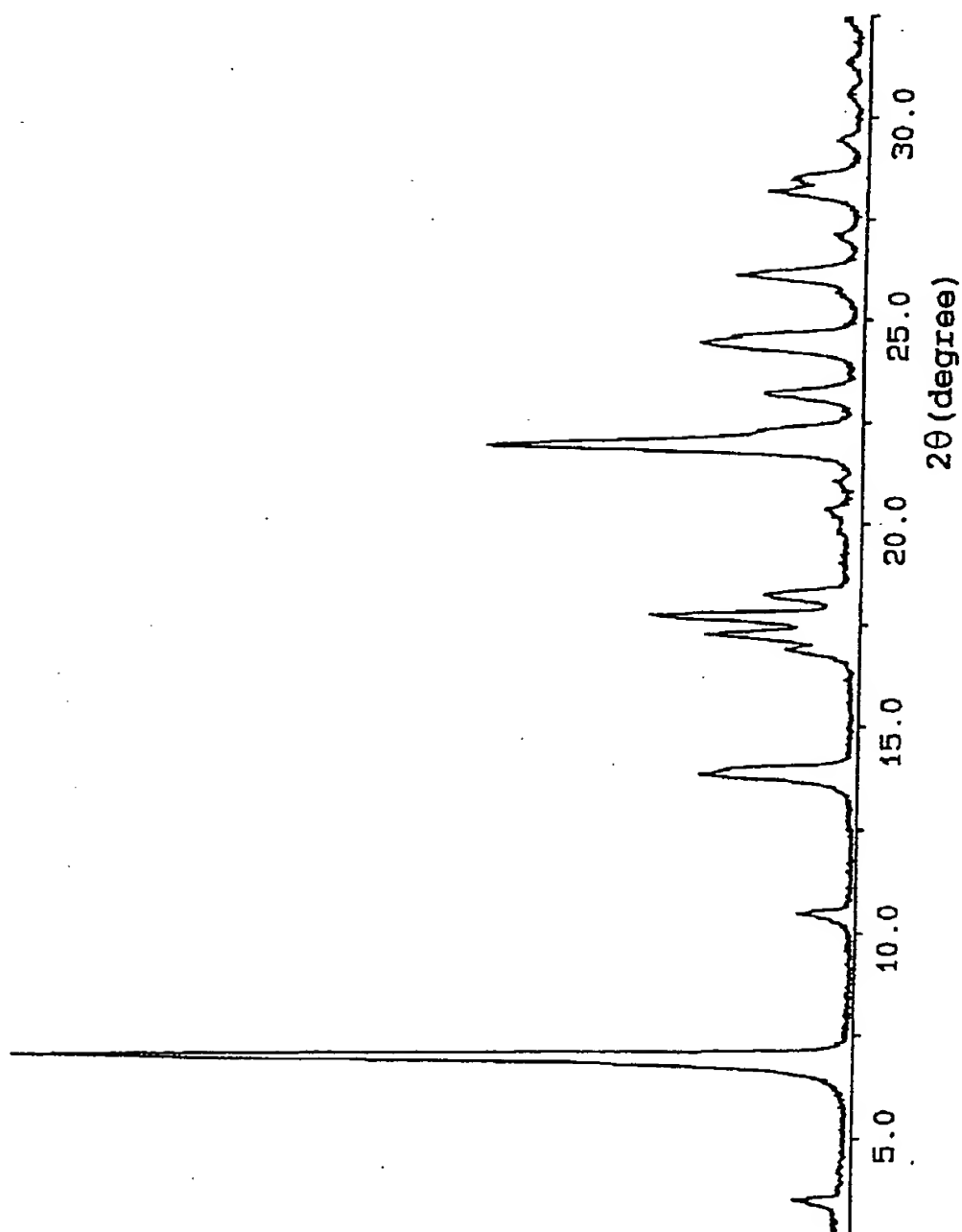
1/5

Fig. 1:



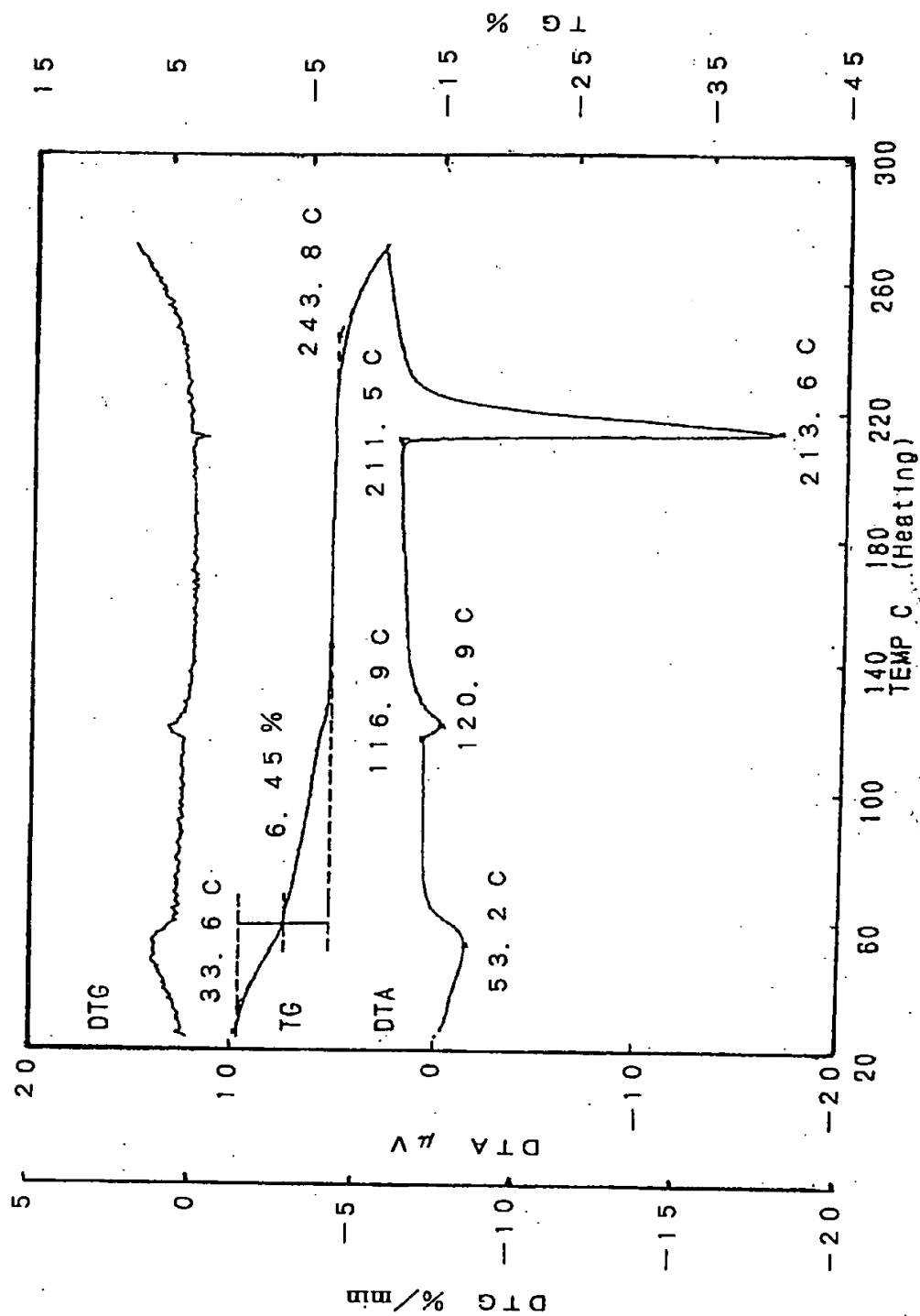
2/5

Fig. 2:



3/5

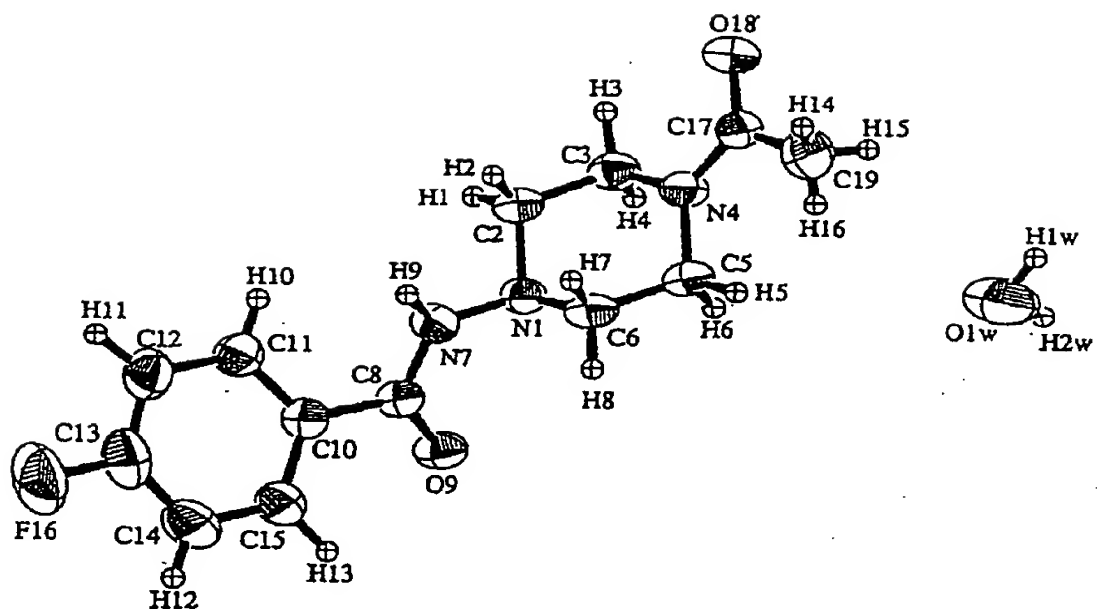
Fig. 3:



差替え用紙 (規則26)

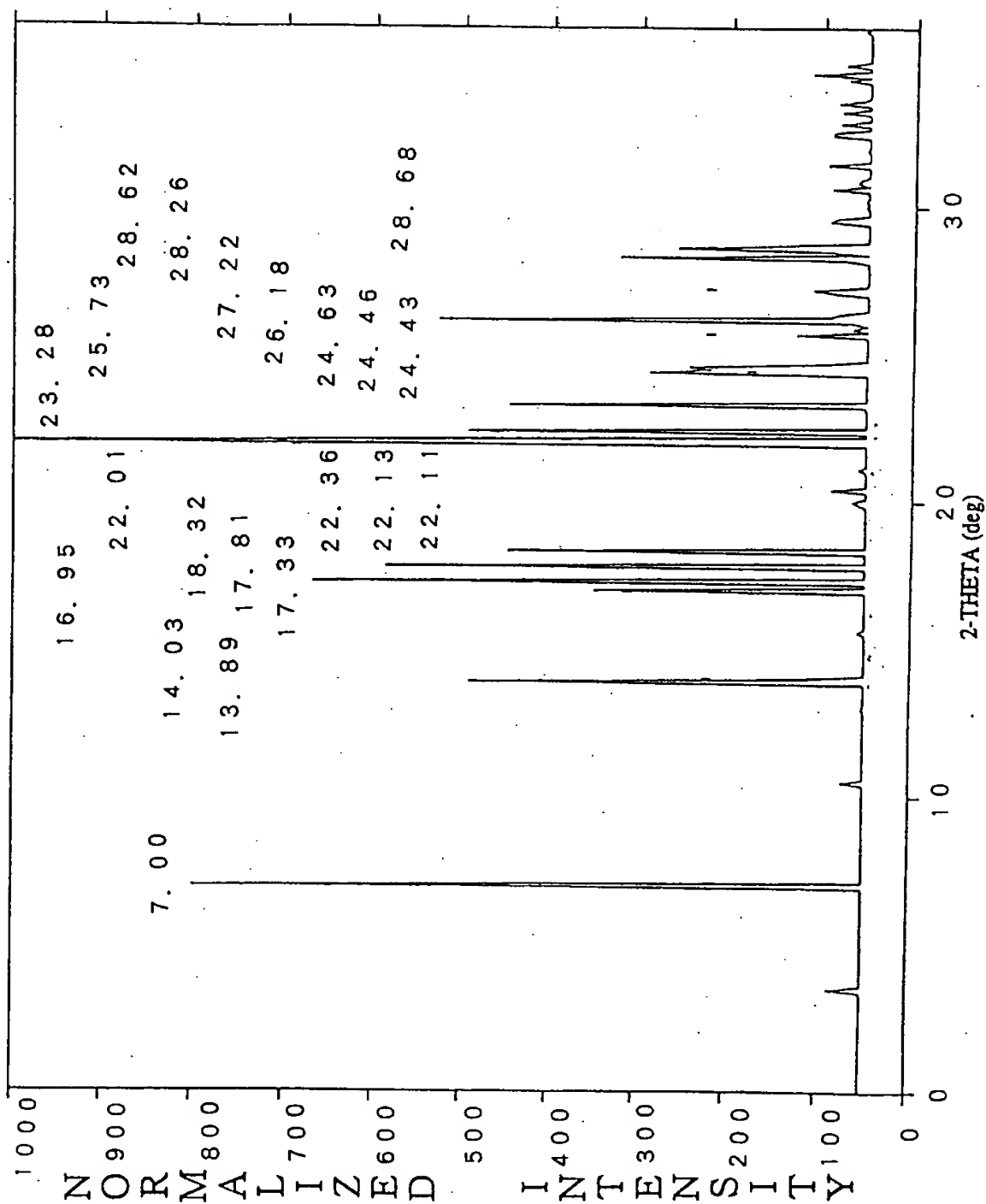
4/5

Fig. 4:



5/5

Fig. 5:



差替え用紙 (規則26)

INTERNATIONAL SEARCH REPORT

Internat : Application No

PCT/JP 97/04451

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D295/32 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 436 734 A (FUJISAWA PHARMACEUTICAL CO) 17 July 1991 see the whole document & WO 91 01979 A cited in the application -----	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

19 February 1998

Date of mailing of the international search report

27. 03. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

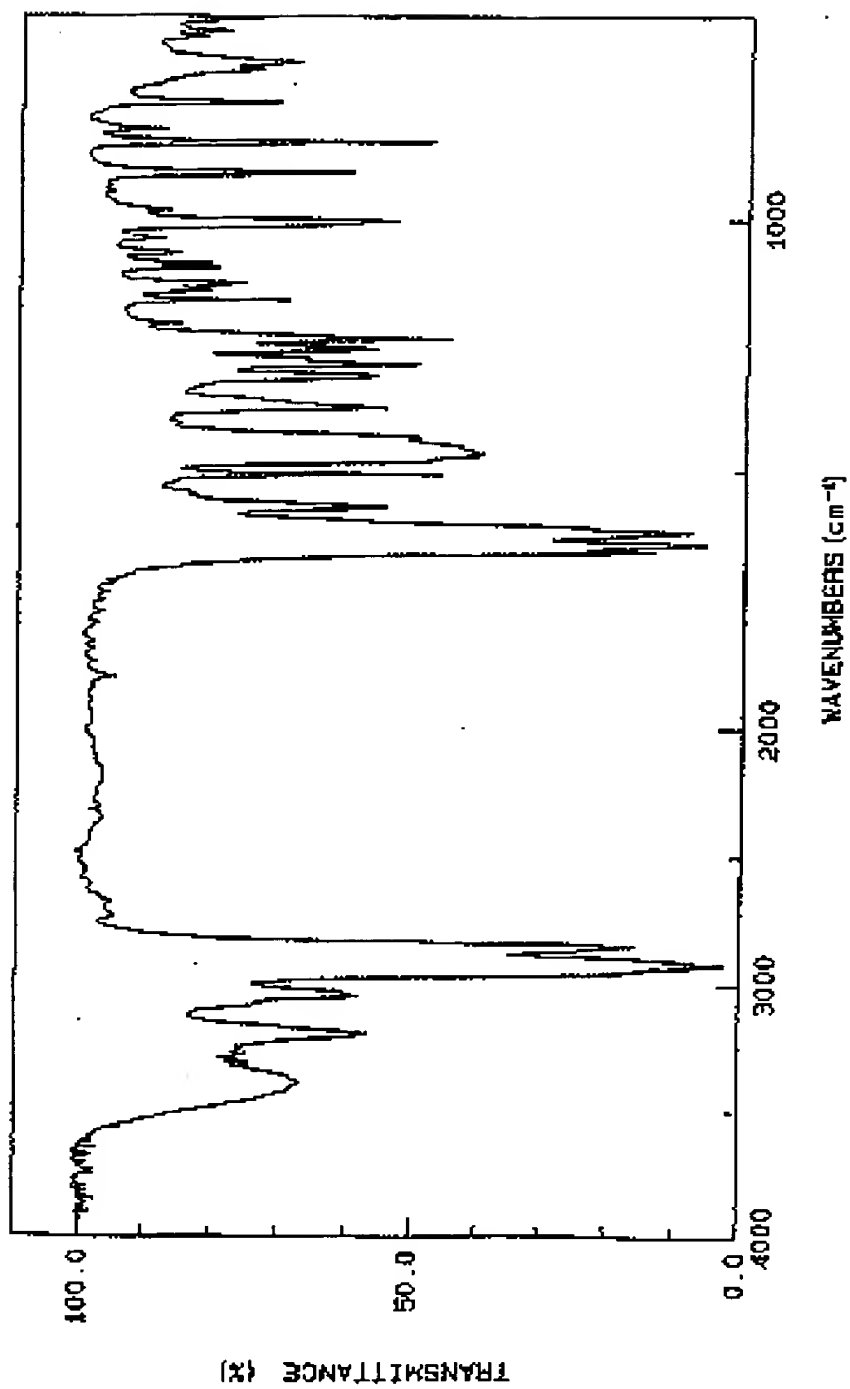
Internal Application No

PCT/JP 97/04451

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0436734 A	17-07-91	DE 69022965 D	16-11-95
		DE 69022965 T	04-04-96
		HK 64196 A	19-04-96
		WO 9101979 A	21-02-91
		JP 2531304 B	04-09-96
		US 5250528 A	05-10-93

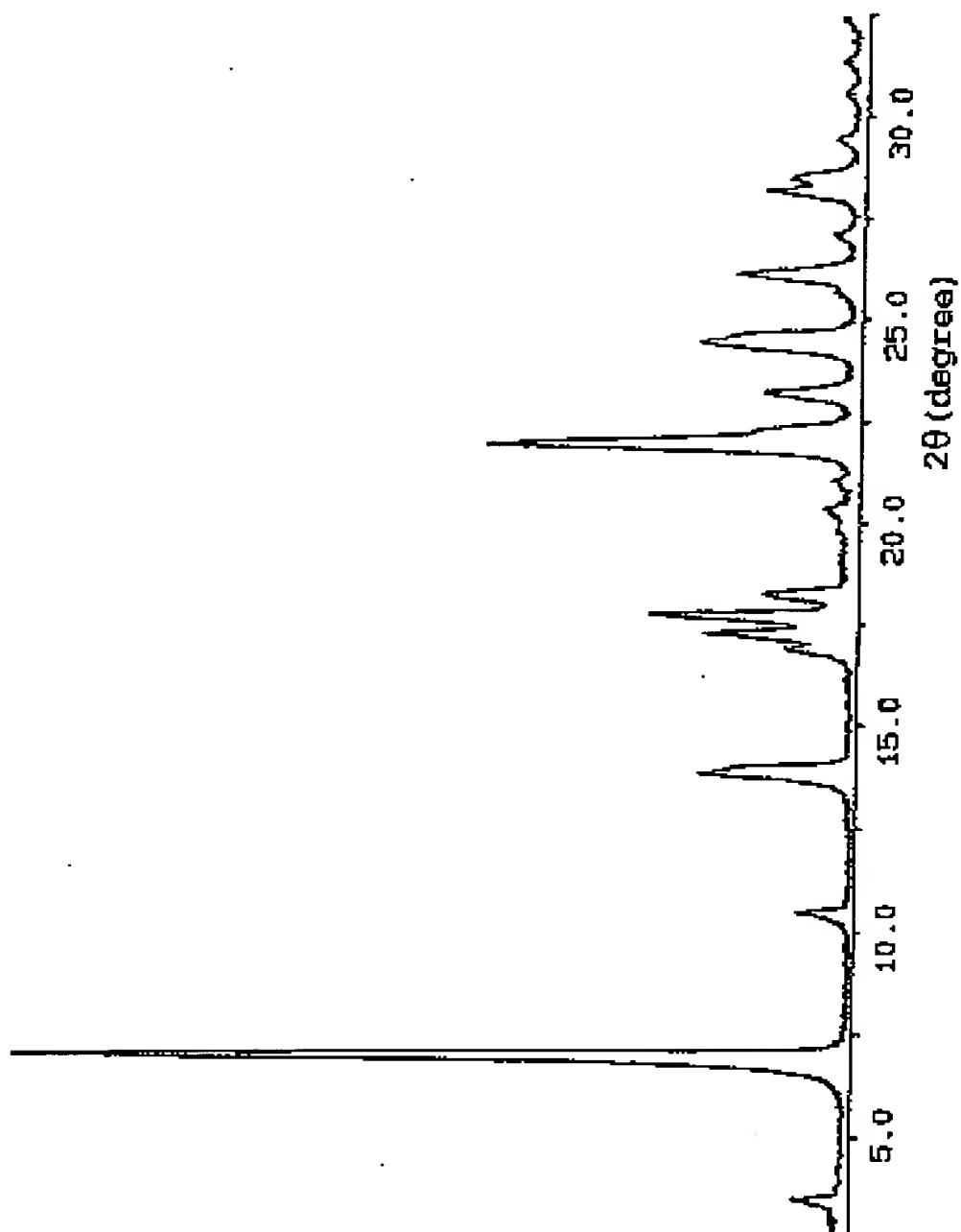
1/5

Fig. 1:



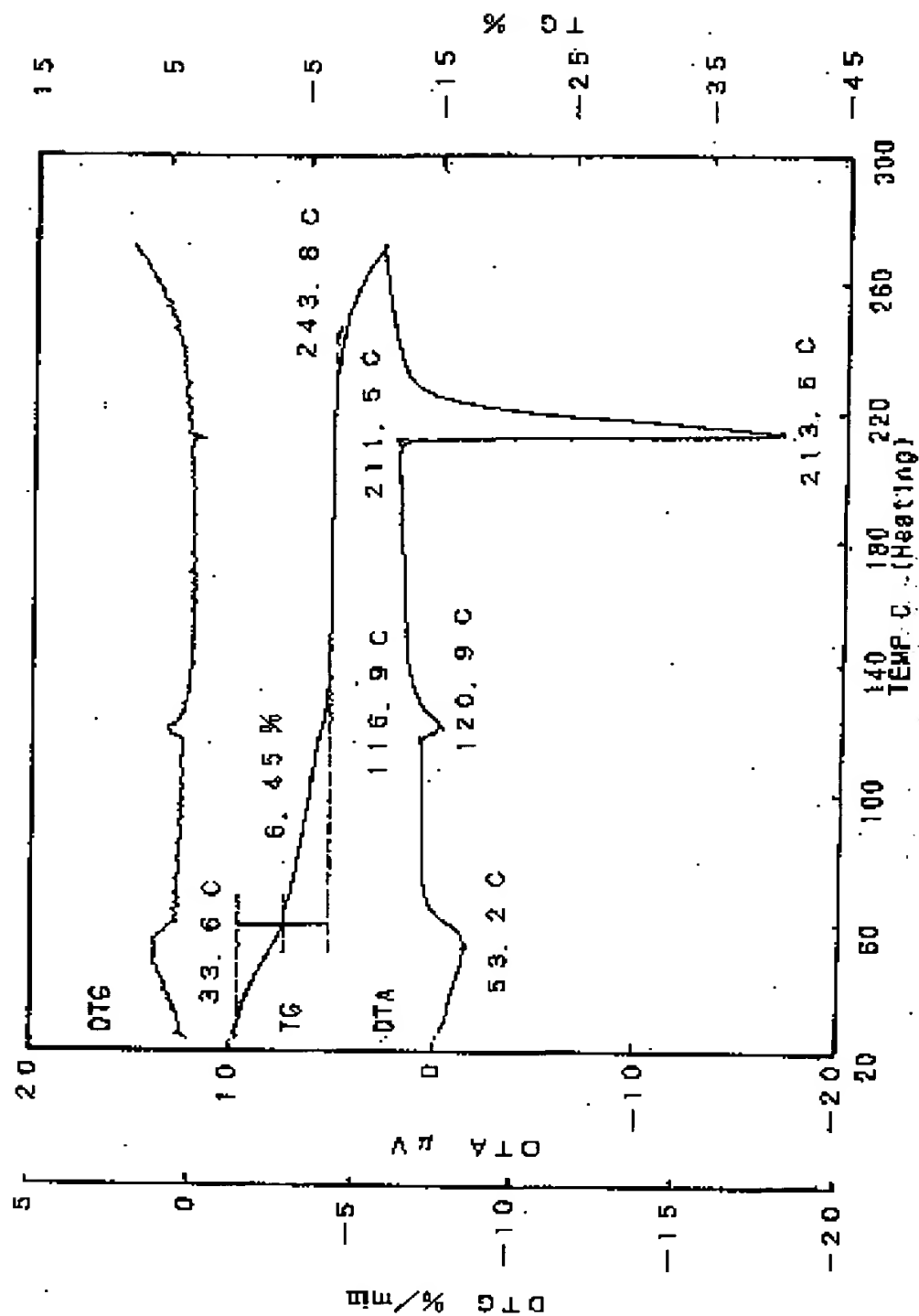
2/5

Fig. 2:



3/5

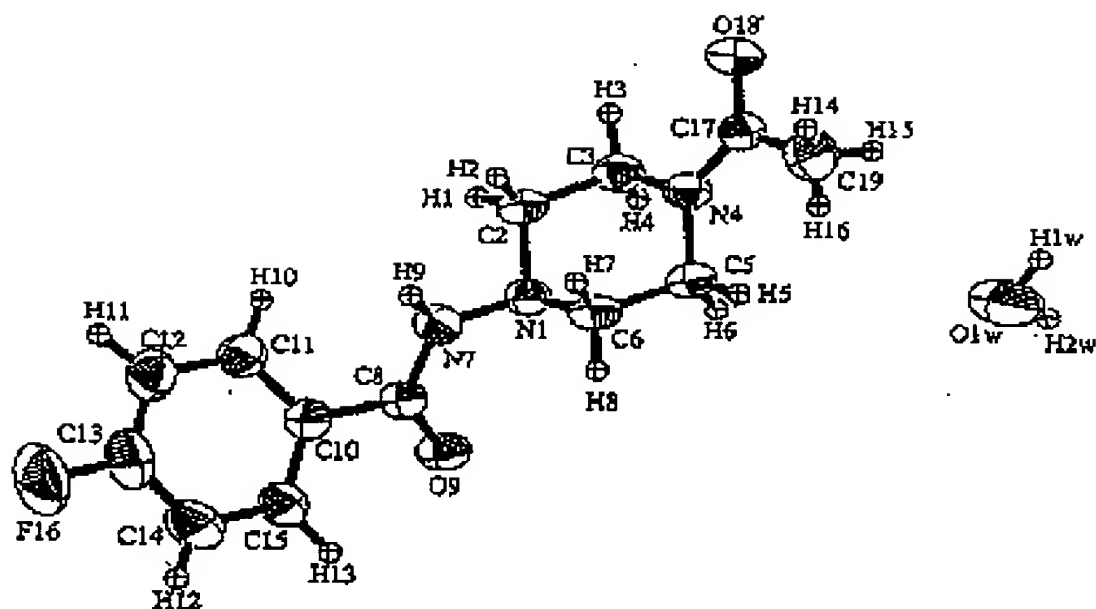
Fig. 3:



差替え用紙 (規則26)

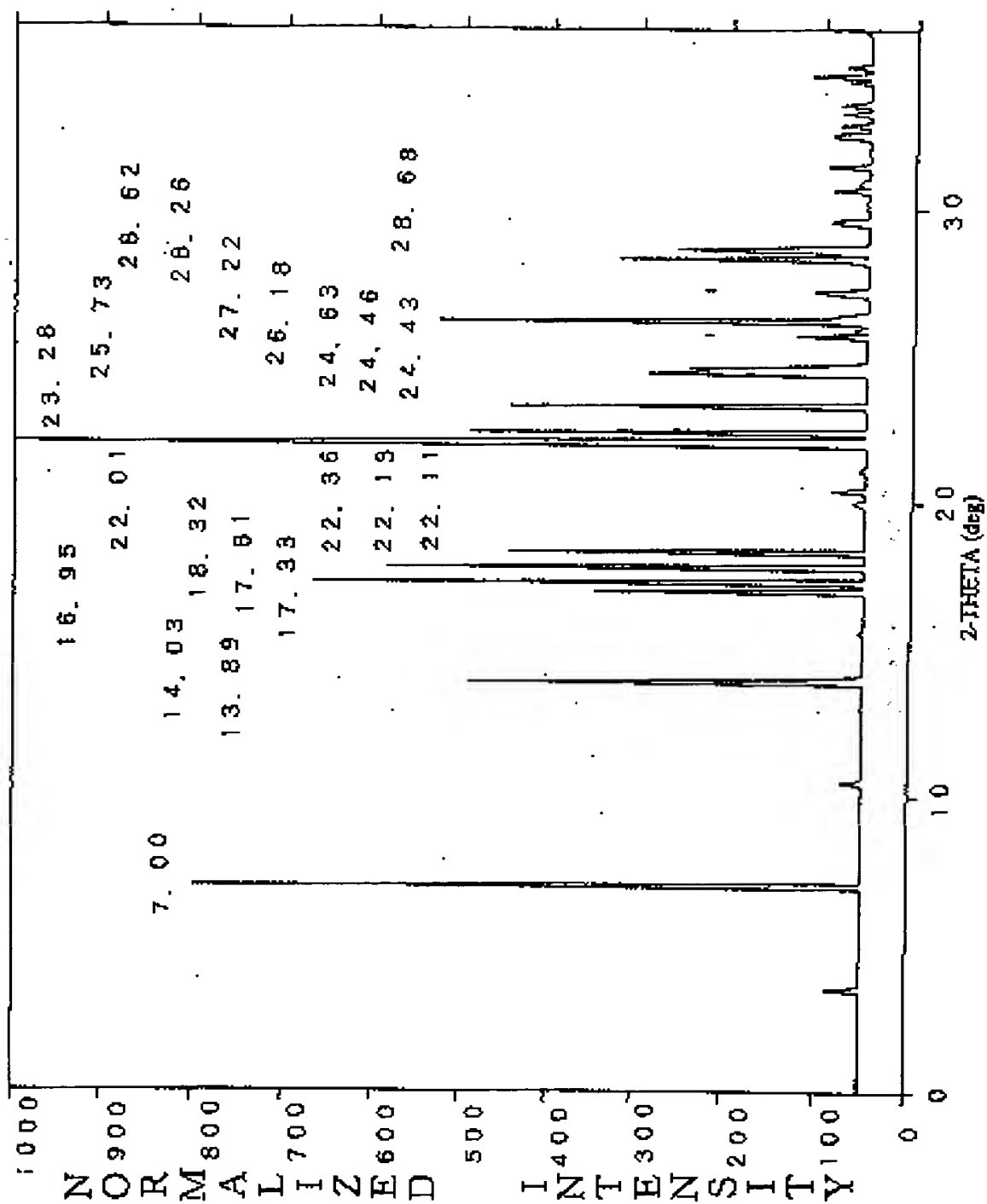
4/5

Fig. 4:



5/5

Fig. 5:



差替え用紙 (規則26)

